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(54) Biocidal or biostatic compositions containing 3-isothiazolones, their method of preparation and their uses.

(57) Biocidal or biostatic compositions containing one or more of a specified range of 3-isothiazolone(s), especially 5-chloro-2-methyl-4-isothiazolin-3-one and/or 2-methyl-4-isothiazolin-3-one, more especially a mixture of the two containing 60-90 weight percent of the chloro compound, having an impurity content (if any) of nitrosamine(s) plus nitrosamine precursor(s) less than 15 ppm, preferably 7.5 ppm, more preferably 3 ppm (on a weight basis) of the 3-isothiazolone(s) and nitrosating agent(s), such as nitrate salt ringstabiliser(s) capable of converting the precursor(s) to nitrosamine(s). The compositions can be made by processes involving purification of intermediate product(s) by ion exchange, recrystallization and/or solvent extraction and/or involving the use of nucleophilic scavenger(s) in the preparation of intermediate product(s) and/or involving the use of certain mercapto-amide(s) as intermediate products. Cosmetic (including toiletry) and pharmaceutical preparations containing the compositions are also disclosed.

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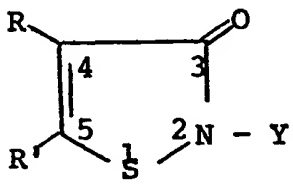
BIOCIDAL OR BIOSTATIC COMPOSITIONS CONTAINING 3-ISOTHIAZOLONES, THEIR METHOD OF PREPARATION AND THEIR USES.

This invention is concerned with biocidal or biostatic compositions containing 3-isothiazolones, their method of preparation and their uses, for example, in cosmetic (including toiletry) and drug (i.e. pharmaceutical) preparations.

The 3-isothiazolones concerned in this invention are known and are of Formula I below:



(I)

wherein R and R' are the same or different and represent hydrogen, halogen (preferably chlorine) or (C_1-C_4)alkyl and Y is (C_1-C_8)alkyl, (C_3-C_6)-cycloalkyl, aralkyl of up to 8 carbon atoms (eg benzyl or phenylethyl) or optionally substituted phenyl.

The compounds of Formula I exhibit biocidal or biostatic activity towards many pest organisms of both animal and vegetable origin such as fungi (eg mildew), bacteria, algae, slime, and molluscs (eg barnacles).

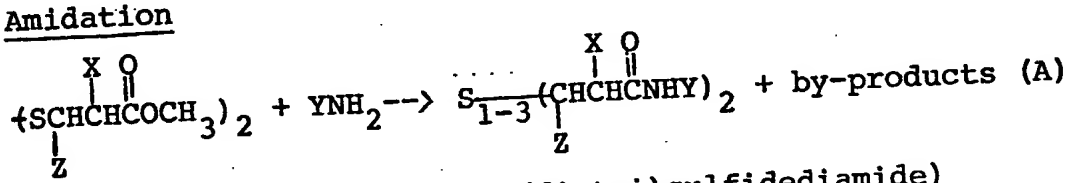
When the 3-isothiazolone of Formula I is one in which Y is (C_1-C_4)alkyl, and at least one of R and R' is halogen (with the other, usually R, hydrogen), the compounds are useful industrial biocides having almost unlimited solubility in water (see U.S. Patent 4,105,431). The less water-soluble, higher alkyl-substituted 3-isothiazolones are generally useful as mildewcides and

fungicides in organic solutions and polymer emulsion products such as paints. The higher alkyl-substituted isothiazolones are soluble in various organic solvents such as ethanol, isopropanol and acetone and such solutions may be easily extended with water. Isothiazolones can also be used in solid formulations, preferably absorbed on or in a particulate carrier.

Unfortunately, solutions of the 3-isothiazolones, especially aqueous solutions or solutions in polar organic solvents such as alcohols, are unstable, leading to reduced biological effectiveness. This is especially true of the compounds of Formula I where Y is (C_1-C_4)-alkyl or (C_3-C_6)cycloalkyl. The instability results from an opening of the isothiazolone ring to form linear compounds which do not have the same biological properties as the ring compounds. To inhibit ring cleavage, nitrate salts (such as those of metals such as calcium, copper, magnesium, manganese, nickel, zinc sodium, potassium, iron, barium, cobalt or mixtures of these) can be added to isothiazolone solutions. Thus it is commercially desirable today to formulate many of the 3-isothiazolone biocides in solutions containing water or polar organic solvent or mixtures thereof together with nitrate stabilizers to prevent decomposition of the 3-isothiazolone (see U.S. 3,870,795).

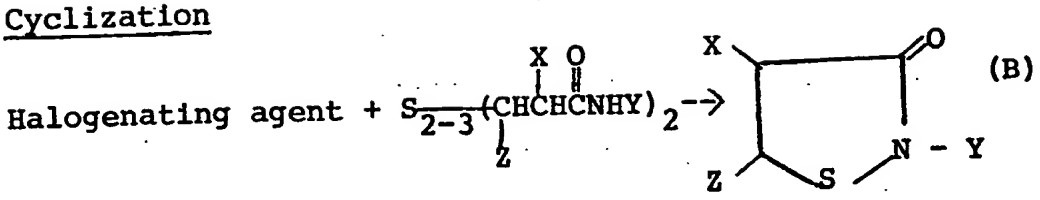
The process used for manufacturing 3-isothiazolones involves amidation of a disulfide followed by the halogenation cyclization of the diamide product as shown below:

Amidation



(disulfide) (amine) (mono(di,tri)sulfidediamide)

Cyclization



(3-isothiazolone)

wherein X and Z (R and R' in the general formula, except for halogen later attached during cyclization) are hydrogen or (C_1-C_4)alkyl and Y is as defined in Formula I.

Cyclization is accomplished by contacting the diamide with a halogenating agent. Typical halogenating agents include chlorine, bromine, sulfuryl chloride, sulfuryl bromide, N-chlorosuccinimide, N-bromosuccinimide, and the like. Chlorine and sulfuryl chloride are the preferred halogenating agents. The amidation of the disulfide intermediate (hereinafter "disulfide") produces the mono(di,tri)sulfidediamide intermediates (hereinafter "diamide") and ultimately the 3-isothiazolone compounds. When prepared according to the above reactions (A) and (B), the 3-isothiazolone component (ie the active ingredient which is herein abbreviated as "AI") is generally a mixture comprising two or more different 3-isothiazolone species of Formula I together with various by-products, including some amines which have not heretofore been characterized.

We have now discovered that certain 3-isothiazolone biocides produced using the prior art disulfide intermediate may contain by-product impurities having a secondary or tertiary amine group which, upon exposure to nitrosating conditions, can be converted to nitrosamines which are generally suspected to be possible carcinogens and therefore undesirable especially in preparations to be used in applications where human or animal contact is anticipated.

The nitrosamine problem is exacerbated when 3-isothiazolone are present in solutions, either aqueous solutions or organic solutions or mixtures thereof, wherein it is necessary to incorporate, as ring stabilizer, a nitrate salt, see, e.g., U.S. Patent 4,067,878, or where another nitrosating agent may be present in the isothiazolone composition. When a metal nitrate salt is present as a stabilizer, any by-product secondary or tertiary amine compound present in the 3-isothiazolone reaction mixture is capable of being nitrosated to a nitrosamine.

There follows a description of the process for preparing 3-isothiazolones which utilizes a disulfide intermediate. In such description and elsewhere in this specification quantities are on a weight by weight basis unless stated otherwise.

In preparing 3-isothiazolone industrial biocides by amidation of the usual disulfide intermediates (e.g., dimethyl-3,3-dithiodipropionate), there are found typical levels of nitrosamine precursors between about 0.5% (5,000 ppm) and about 1.1% (11,000 ppm) by weight in the diamide product. After the diamide product is cyclized with a halogenating agent, filtered, neutralized, dissolved in water together with a metal nitrate stabilizer and heat-treated to remove by-product impurities, the final product contains about 6% - 16% (by weight of the original precursor) of a nitrosamine. For example, in the case of an original precursor content of 5,000 ppm, the final product (see Experiment 1 below) has been found to contain typically 750 ppm of nitrosamine. Because of the high dilution factor in industrial applications, under use conditions the nitrosamine is rarely present in concentrations greater than parts per billion.

Among the most effective biocides for inhibiting bacterial growth are those containing one or both of

the 3-isothiazolones of Formula 1 wherein R is hydrogen, R' is hydrogen or chlorin and Y is methyl, especially a 3-isothiazolone mixture comprised mainly of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one (mixture dependent upon chlorination (cyclization) conditions), more especially wherein the chlorinated species is between 60% and 90% by weight of the total active ingredients (AI). The process of manufacture includes the following:

Amidation

$$(SCH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3)_2 + 2\ CH_3NH_2 \xrightarrow{\text{(toluene)}}$$

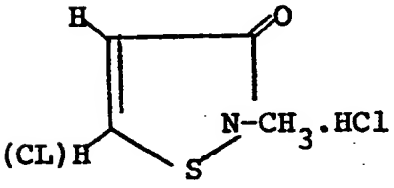
(disulfide)

$$S_n(CH_2CH_2\overset{O}{\overset{\|}{C}}NHCH_3)_2 + 2CH_3OH + \text{by-products } (\tilde{=}5\%) \quad (1)$$

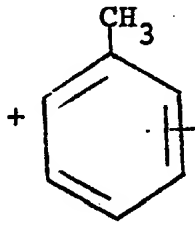
(diamide) (n = 1, 2, 3)

Chlorination (Cyclization)

$$S_{2-3}(CH_2CH_2\overset{O}{\overset{\|}{C}}NHCH_3)_2 + Cl_2\ (3\text{-}6\text{ moles}) \xrightarrow{\text{(solvent)}}$$

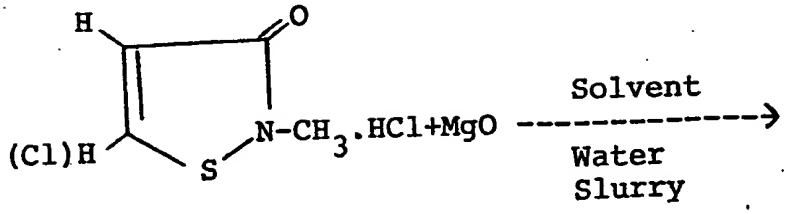


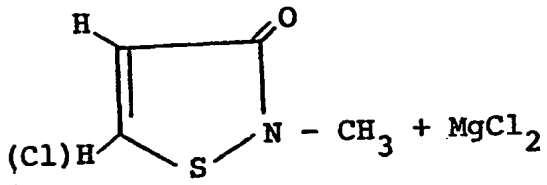
(isothiazolone hydrochloride)



+ Cl + HCl (2)

Neutralization





(3)

3-isothiazolone

(technical grade)

The first reaction above (1) produces a mixture containing about 95% mono-, di- and tri-thiodiamides and methanol. Upon cleavage of the disulfide (during amidation), N-methylacrylamide by-product is believed to be formed. Conjugate addition of monomethylamine to this cleavage by-product may lead to the formation of the nitrosamine precursor, N-methyl-3-(N'-methylamino) propionamide, by the following probable reaction:

$$CH_3NH_2 + CH_3NHCOCH{=}CH_2 \longrightarrow CH_3NHCH_2CH_2CONHCH_3 \quad (4)$$

(nitrosamine precursor, MMAP)

N-methylacrylamide will also theoretically add to MMAP produced by reaction (4) above according to the following:

$$CH_3NHCH_2CH_2\overset{O}{\overset{\|}{C}}NHCH_3 + CH_3NHCOCH{=}CH_2 \longrightarrow \quad (5)$$

$$CH_3NHCOCH_2CH_2\overset{CH_3}{\overset{|}{N}}CH_2CH_2CONHCH_3$$

(nitrosamine precursor)

Both of the above nitrosamine precursors, particularly MMAP have been identified as being present in the intermediate amide produced when amidating a disulfide starting material. The nitrosamine precursors remain with the AI through chlorination, neutralization and formulation of the 3-isothiazolone composition until the metal nitrate salt is added, at which time nitrosation takes place, principally during heat treatment, (or alternatively during storage) to form a nitrosamine, e.g.:

$$CH_3NHCH_2CH_2CONHCH_3 + NO\cdot X \xrightarrow{pH\ 2\text{-}3} CH_3\overset{NO}{\overset{|}{N}}CH_2CH_2CONHCH_3 \qquad (6)$$

The amidation reaction (1) is conducted in an organic solvent, either aliphatic or aromatic or mixtures thereof. Illustrative of the solvents used are methanol, toluene and Laktane. Laktane is a commercial (Exxon) hydrocarbon solvent with a flash point of 25°F, a b.p. range of 102-108°C, and having the composition:

paraffins	28% w/w
cycloparaffins	54% w/w
toluene	18% w/w

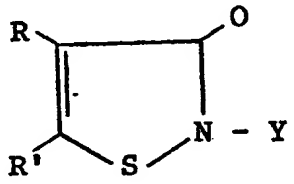
The diamide reaction mixture resulting from amidation has a high solids content. Chlorination of the filtered diamide mixture to form the cyclic 3-isothiazolone hydrochloride mixture (2) is conducted with the diamide in a concentrated slurry in an organic solvent typically toluene, perchloroethylene, ethyl or tributyl acetate, the reaction preferably involving the concurrent feeding of the diamide slurry and chlorine gas in the proper molar ratio (3-6, preferably 5, mols Cl_2/1 mol of amide) to a reactor.

An aqueous slurry of magnesium oxide may be used

to neutralize the filtered 3-isothiazolone hydrochloride r action mixture to form the technical grade product. A metal nitrate stabilizer compound is subsequently added to the technical grade product prior to a final heat treatment step. Heat treatment is effective for removing or decomposing by-products.

It has now been discovered that nitrosamines can be substantially eliminated from 3-isothiazolone products by (I) removing nitrosamine precursor(s) from the diamide intermediate reaction mixture or by (II) inhibiting formation of nitrosamine precursor(s) during the amidation reaction. Alternative processes have been developed for each of (I) and (II).

Accordingly the invention provides a biocidal, or biostatic composition containing (1), as an active component, at least one 3-isothiazolone, (2) a medium for the 3-isothiazolone and (3) a nitrosating agent capable, on treating the composition, of converting, to a nitrosamine, any nitrosamine secondary or tertiary amine precursor present therein, said 3-isothiazolone being of Formula I below:



(I)

wherein R and R' are the same or different and represent hydrogen, halogen or (C_1-C_4)alkyl and Y is (C_1-C_8)alkyl, (C_3-C_6)cycloalkyl aralkyl of up to 8 carbon atoms or optionally substituted phenyl groups, and characterised in that the impurity content, if any, in the composition of nitrosamine(s) plus nitrosamine precursor(s) is less than 15 ppm (on a weight basis) of 3-isothiazolone(s) of Formula I.

Preferably the nitrosating agent is a nitrate salt present in an amount sufficient to stabilize the 3-isothiazolone against ring cleavage.

The impurity content is preferably less than 7.5 ppm. In an especially preferred embodiment the impurity content is less than 3 ppm.

Stabilized 3-isothiazolone compositions, as sold for dilution, usually contain substantially 15% AI and such compositions (being also compositions in accordance with the invention - see Examples) will contain less than 100 ppm (preferably less than 50 ppm and even more preferably less than 20 ppm) of precursors and nitrosamines. As will be demonstrated hereinafter, it is even possible to produce compositions with no detectable nitrosamine or precursor compounds. The above quoted figures of 100, 50 and 20 ppm of a composition containing 15% AI correspond to figures of 15, 7.5 and 3 ppm based on AI.

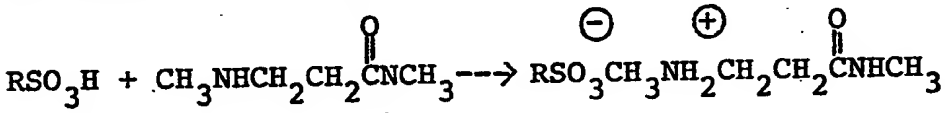
Removal or partial removal of the precursor(s) from the diamide intermediate may be accomplished by separation techniques such as (a) ion exchange, (b) crystallization or recrystallization, or (c) solvent extraction (filtration and washing). These techniques are useful with the diamide reaction mixture produced from a disulfide intermediate even when this is carried out in the presence of a nucleophilic scavenger as disclosed later or when utilizing a mercaptan as intermediate as disclosed later for inhibiting formation of the nitrosamine precursor. When the 3-isothiazolone product must be essentially nitrosamine-free, it may be preferred to use a combination of the process using a mercaptan and one or more of the above precursor removal techniques.

Recrystallization of N,N'-dimethyl-3,3'-dithiodepropionamide, from 2-propanol effectively removes the

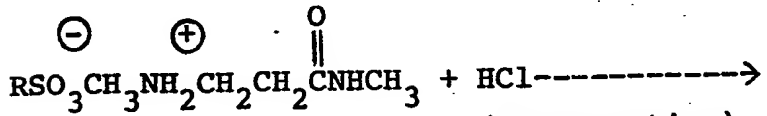
nitrosamine precursor N-methyl-3-(N'-methylamino) propionamide from the reaction mixture of the disulfide and methylamine (see Example 1 below).

Filtration and methanol washing of the N,N'-dimethyl-3,3'-dithiodiprionamide wetcake (see Example 3, below) reduces the precursor N-methyl-3-(N'-methylamino) propionamide level from 5000 ppm to 400 ppm.

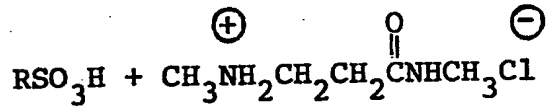
Removal from the diamide of the nitrosamine precursor by selective ion exchange of the reaction mixture is also effective (see Examples 4 and 5 below). Treatment of a methanolic solution of N,N'-dimethyl-3,3'-dithiodipropionamide with a sulfonic acid cation exchange resin (Amberlyst 15, Amberlyst being a trademark of Rohm and Haas Company) provides good removal of N-methyl-3-(N'-methylamino)propionamide from the reaction mixture of the disulfide with monomethyl amine (see reaction 1, above). The resin may be regenerated with methanolic aqueous hydrogen chloride. The ion exchange process may be represented as follows:



(Resin) (precursor)



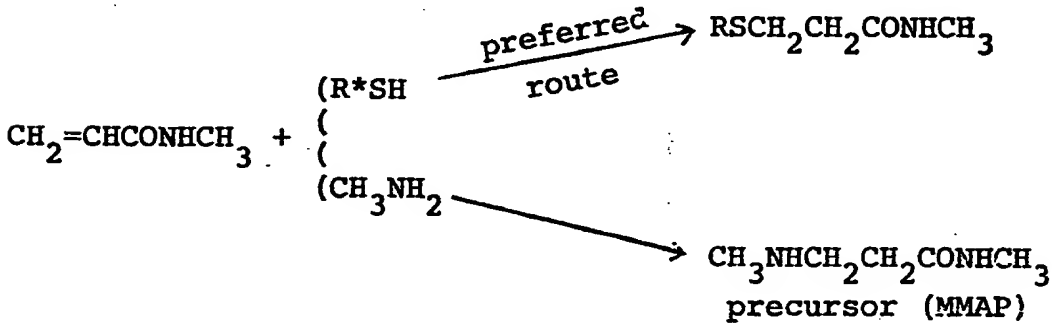
(regeneration)



The final product 3-isothiazolone made from the ion exchange-treated intermediate has a much reduced nitrosamine content.

Formation of the nitrosamine precursors can be inhibited by use of a nucleophilic scavenger during the

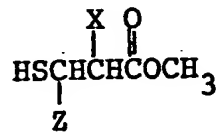
amidation reaction or by selection of different intermediates for the amidation reaction. Useful nucleophilic scavengers are materials which are generally (a) more active than an amine in a Michael addition reaction but (b) which do not degrade the reactants or reaction product of the amidation (see Example 6 below). Most aliphatic and aromatic mercaptans are useful scavengers in relation to the addition reaction to N-alkylacrylamide intermediates, which are the reactive compounds responsible for producing the principal nitrosamine precursors (see reactions 4 and 5 above). Other Michael addition reactants, such as sodium or potassium salts of alcohols are generally not as desirable because of their high reactivity with other starting materials. A higher concentration of the nucleophilic scavenger in the amidation reaction leads to proportionally greater reduction of the nitrosamine precursors:



R* = e.g., methyl, ethyl, propyl, phenyl, etc. and also $-CH_2CH_2COA-$(alkyl) where A = O or NH.

The inherent avoidance of nitrosamine precursor when a mercaptan intermediate is selected in place of the normal disulfide intermediate in the amidation

reaction is an important and unexpected finding of the present invention. A preferred mercaptan intermediate has the formula:



wherein X and Z have the meaning set forth above. The intermediate is essentially half of the conventional disulfide reactant (see reaction A above) used in the amidation reaction but, surprisingly, yields a product much lower in nitrosamine precursor, presumably by the same mechanism as postulated above for the nucleophilic scavengers. In the case of the isothiazolone biocide mixture illustrated above (in reaction 1-3) the mercaptan which may be used has the formula $HSCH_2CH_2COOCH_3$ and is referred to as "MMP" (methyl-3-mercaptopropionate). The remarkable reduction in nitrosamine precursor in the amide when using MMP in place of the usual disulfide is illustrated in the following table:

TABLE I

Precursor* ($CH_3NHCH_2CH_2CONHCH_3$) Level in Intermediate Compared to MMP Process Intermediate

Amidated Disulfide Intermediate (Reaction 1 above)

Intermediate Batch	Precursor in Amide Reaction Mixture (ppm)
1	5,600
2	4,800
3	6,400
4	4,500
5	5,000
6	10,100
7	11,400
8	5,700
9	9,400
10	6,700

Amidated MMP Intermediate ($HSCH_2CH_2CONHCH_3$)

Intermediate Batch	Precursor in Amide Reaction Mixture (ppm)
1, 2, 3	21, 24, 31
4	43
5	37
6	80
7	60
8	70
9	<30
10	<30
11	110

* Precursor = MMAP (see reaction 4, above).

Other advantages of using a mercaptan intermediate (e.g., MMP) may be found in the reaction product of the mercaptan and the amine. In the case of MMP, the amide is a liquid rather than a solid, as is the case with a disulfide intermediate. The difficulties usually encountered in handling, agitating, pumping and reacting a slurry are thus avoided. Further, use of the mercaptan intermediate reduces the amount of halogen (chlorine) needed for cyclization of the amide from the usual 3.0-6.0 mols/mol of intermediate to 2.8-3.4 mols, preferably 3.0 mols, per mol of intermediate.

The nitrosamine precursor by-product of the amidation reaction carries through to the final product, but the dilution of the AI in the product results in a lower concentration. Thus, the ultimate stabilized 3-isothiazolone composition will normally have a nitrosamine concentration of about 15% of the precursor concentration found in the amide. Table II illustrates the different concentrations of the major nitrosamine precursor (MMAP) in the amide compared to the nitrosamine (MMNP) in the corresponding stabilized (nitrate added/heat treated) product for a mixture containing (as the AI) 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one produced from an MMP starting material of the present invention.

TABLE II

Precursor (MMAP) in Amide Interm diate v. Nitrosamine in Stabilized Product

Amide Intermediate		Stabilized 3-Isothiazolone	
Sample No.	MMAP (ppm)		MMNP* (ppm)
1	80		<3
2	<30		2.0
3	60		<1.0
4	70		7.3
5	<30	**	2.3
			3.8
6	<30		1.9
7	110		10.6
		**	3.4
			8.3
8	21	**	1.0
			1.0
9	24		1.0
10	31	**	1.0
			2.0
11	31		10.3
12	43		11.6
		**	7.9
			3.6
13	37		6.0
		**	5.3
			5.6

*MMNP = N-methyl-3-(N'-methyl-N'-nitroso) aminopropionamide.

**Intermediate divided for multiple conversions to the final product.

The mechanism for nitrosamine reduction in the above MMP process appears to reside in the reduction of the nitrosamine precursor N-methyl-3-(N'-methyl) aminopropionamide (MMAP) in the amide. The amide disulfide source for the postulated N-methylacrylamide intermediate (reaction 4 above) is reduced to a minor reaction by-product. Also, the MMP starting material and N-methyl-3-mercaptopropionamide appear to compete successfully with monomethylamine to consume N-methylacrylamide and hence avoid formation of MMAP. These postulated alternative routes are as follows:

$$CH_3NHCOCH=CH_2 + HSCH_2CH_2CO_2CH_3 \longrightarrow CH_3NHCOCH_2CH_2SCH_2CH_2CO_2CH_3$$

$$CH_3NHCOCH=CH_2 + HSCH_2CH_2CONHCH_3 \longrightarrow (CH_3NHCOCH_2CH_2)_2S$$

The net result is the reduction of MMAP levels from about 5,000-11,000 ppm for the disulfide process to about <100 ppm in the MMP process.

The heat treatment carried out after the addition of the nitrate stabilizer is preferably performed for a duration and at a temperature and pressure such as will result in the same degree of by-product removal or decomposition as would be achieved by a heat treatment for 4 hours at 95°C and under atmospheric pressure.

The following comparative experiments and examples are offered to illustrate this invention.

EXPERIMENT 1 (Comparative experiment using a disulfide intermediate)

Step 1: Amidation Preparation of N,N'-dimethyl-3,3'-dithiodipropionamide Intermediate

Charged to a vapor-tight reaction kettle was dimethyl-3,3'-dithiodipropionate 45.8 kg (101 lb, 0.424 mol), laktane 59.4 kg (131 lb) and methanol 2.3 kg (5.06 lb). The mixture was cooled to 15-20°C with agitation. Monomethylamine 14.9 kg (32.8 lb. 1.06 mol) was added beneath the surface of the reaction mixture with agitation at 15-20°C and 351-703 kg/m^2 (5-10 psi) over 2 hr. After completing the monomethylamine addition, the mixture was stirred at 15-20°C for 10 hr. A thick, pale-yellow slurry was obtained. At this time the unreacted monomethylamine and methanol by-product were distilled from the mixture at ~100 mmHg. After the distillation period. the yellow slurry was rotary vacuum dried and isolated without washing to provide crude, dry N,N'-dimethyl-3,3'-dithiodipropionamide 45.4 kg (100 lb, 100% yield), containing 5,000 ppm N-methy-3-(N'-methyl) aminopropionamide.

Step 2: Chlorination (cyclization)

Preparation of a mixture of 5-chloro-2-methyl-4-isothiazolin-3-one hydrochloride and 2-methyl-4-isothiazolin-3-one hydrochloride.

A slurry of the crude N,N'-dimethyl-3,3'-dithiodipropionamide reaction product of Step 1 was diluted with toluene and chlorinated to yield a slurry containing 5-chloro-2-methyl-4-isothiazolin-3-one hydrochloride and 2-methyl-4-isothiazolin-3-one hydrochloride and mother liquor.

Step 3: Filtration and Neutralization

The chlorinated slurry from Step 2 was filtered and neutralized with a magnesium oxide slurry to form the technical grade product.

Step 4: Formulation and Heat Treatment (Stabilization)

The technical grade product made in Step 3 was formulated by adding magnesium nitrate hexahydrate, and transferring the mixture to a heat treatment kettle equipped with an agitator and a reflux condenser. The product was heat treated for 4 hours and then allowed to cool to room temperature. The batch was filtered to remove small amounts of suspended solids. This gave a product with the following AI and nitrosamine analysis:

Components	
5-chloro-2-methyl-4-isothazolin-3-one	9.8% by wt
2-methyl-4-isothazolin-3-one	6.0% by wt
Nitrosamine[a]	750 ppm

[a] N-methyl-3-(N'-methyl-N'-nitroso)aminopropionamide (MMNP).

EXPERIMENT 2 (Further comparative experiment using a disulfide intermediate)

Step 1: Amidation

Into a three-liter, 4-necked flask equipped with a mechanical stirrer, thermometer, gas dispersion tube and dry ice condenser with nitrogen inlet adapter, was placed dimethyl-3,3'dithiodipropionate (1,062.5g, 4.46 mol), toluene (535.0g) and methanol (55.0g). The

apparatus was purged with nitrogen and the mixture was cooled to 10°C. Monomethylamine (346.0g, 11.14 mol) was added through the gas dispersion tube with stirring at 10-20°C over 2 hrs. After completing the monoethylamine addition, the mixture was stirred at 20°C for 20 hrs. to complete the reaction. A thick, pale yellow slurry was obtained. At this time the unreacted monomethylamine and methanol by-product were distilled from the mixture at ~100mmHg. The crude dry N,N'-dimethyl-3,3'-dithiodipropionamide intermediate (1,022.4g, 97% yield) contained 11,000 ppm N-methyl-3-(N'-methyl)aminopropionamide.

A portion of the intermediate slurry was filtered, washed with toluene and dried. The dry intermediate contained 8,000 ppm of N-methyl-3-(N'-methyl)aminopropionate.

Step 2: Chlorination

Preparation of a mixture of 5-chloro-2-methyl-4-isothiazolin-3-one hydrochloride and 2-methyl-4-isothiazolin-3-one hydrochloride.

A one-liter 3-necked round bottom flask was equipped with an overhead agitator, a feed line (outlet) and a condenser with a drying tube. Into this flask, 635.8g of a slurry of N,N'-dimethyl-3,3'-dithiodipropionamide (with 8,000 ppm precursor) in toluene was placed and agitated.

A one-liter, 5-necked resin kettle (i.e., a chlorinator) was equipped with an agitator, a fritted glass gas dispersion tube for Cl_2 inlet, a thermometer, a condenser attached to an off-gas scrubber, and a feed line-inlet for intermediate slurry. The kettle was jacketed for ice-water circulation. The cooling system maintained the chlorination batch at 25-30°C. The chlorinator was charged with a 108g of toluene as a heel, and the agitator was started.

The slurry and Cl_2 were fed concurrently at a molar feed ratio of 5.2. Thus, 453g of the slurry was charged over a 55-minute period at a rate of about 8.2g/min., while 227g of Cl_2 (gas) was fed at a rate of about 4.1g/min., using a calibrated flowmeter.

Step 3: Filtration and Neutralization

To the agitated chlorination slurry 20g of water was added gradually. After 10 min. of agitation, the batch was allowed to settle, and the mother liquor was siphoned out using a dipstick. An additional 45g of water was added, and additional mother liquor was removed.

To the hydrochloride wet cake was added 116g of water. The mixture was neutralized to a pH 4.5 by gradually adding an aqueous MgO slurry. The neutralized material was transferred to a separatory funnel and a 469g of an aqueous technical grade material was separated from the organic layer:

Active Ingredient	Wt %
5-chloro-2-methyl-4-isothazolin-3-one	17.1
2-methyl-4-isothiazolin-3-one	5.5

Step 4: Formulation and Heat Treatment (Stabilization)

The pH of the above technical grade material was adjusted to 2.9, and 46.5g of magnesium nitrate hexahydrate and 7.24g of water were added to 100g of the AI with agitation to give a solution with the following composition:

Component	Nominal Conc., Wt %
Total AI	15.2
$Mg(NO_3)_2$	17.4

The above formulated product was transferred to a 500 ml 3-necked round bottom flask equipped with an overhead agitator, a water-cooled condenser and a thermometer attached to a themo-watch and pneumatic pot lifter assembly supporting a heating mantle.

The formulated product was heat-treated at 95°C for 4 hrs. The product, 153.7g, was filtered to remove any trace amounts of solids, and analyzed.

Analysis:

Components	
5-chloro-2-methyl-4-isothiazolin-3-one	10.1 % by wt.
2-methyl-4-isothiazolin-3-one	5.0 by wt.
Nitrosamine*	1200 ppm

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* $CH_3N(NO)-CH_2CH_2CONHCH_3$

EXAMPLE 1

Recrystallization of Crude N,N'-Dimethyl-3,3'-dithiodipropionamide (Removal of Nitrosamine Precursor)

Crude diamide intermediate (disulfide produced as in Experiment 1 above), 1400g, was dissolved in 1750g of boiling 2-propanol and the solution was filtered rapidly through a pre-heated Buchner funnel. The filtrate was kept overnight at 5-10°C in a refrigerator. The crystalline product was collected by filtration on a Buchner funnel, washed with a 560g portion of cool methanol and dried on a rotary evaporator (35°C/20 mm of Hg/2 hours) to give 995g of 99.1% pure intermediate m.p. 113-115°C.

Next, 789.2g of the crystallized diamine intermediate was recrystallized from 2300g of boiling 2-propanol to give 685.6g of 99.9+% w/w amide intermediate, m.p. 113-115°C.

Anal. calcd. for $C_8H_{16}N_2O_2S_2$: C,40.65; H,6.82; N,11.85; O,13.54; S,27.13.
Found: C,40.29; H,6.83; N,11.61; O,13.57; S,27.38.

The N-methyl-3-(N'-methyl)aminopropionamide content was 0 ppm.

(b) Nitrosamine-Free Product, Using Pure Amide Intermediate

Following the chlorination procedure described in Experiment 2, 152.6g of recrystallized pure diamide was chlorinated; the chlorination slurry was filtered and neutralized to give 537.9g of technical grade product, with a total AI of 21.5%.

A 350g portion of this technical grade product was formulated by dissolving 145.5g magnesium nitrate hexahydrate in the product. The formulated product was heat-treated at 95°C for 4 hours to give 495g of 3-isothiazolone composition with the following ingredients:

5-chloro-2-methyl-4-isothiazolin-3-one	10.3% by wt.
2-methyl-4-isothiazolin-3-one	5.0% by wt.
Nitrosamine ppm	0
Nitrosamine precursor(s)	none detected

EXAMPLE 2

Nitrosamine-free Products, from Pure Active Ingredient Isothiazolones

Alternatively, pure 2-methyl-4-isothiazolin-3-one, and pure 5-chloro-2-methyl-4-isothiazolin-3-one, can be obtained and formulated as above to give pure product. This material, with or without the 95°C/4 hour heat treatment, is found to be free of nitrosamines and nitrosamine precursors.

EXAMPLE 3 (Precursor Removal by Solvent Extraction)

Into a three-liter, 4-necked flask equipped with a mechanical stirrer, thermometer, gas dispersion tube and dry ice condenser with nitrogen inlet adapter, was placed dimethyl-3,3'-dithiodipropionate (1062.5g, 4.45 mol) toluene (295.0g) and methanol (295.0g). The apparatus was purged with nitrogen and the mixture was cooled to 10°C. Monomethylamine (304.7g, 9.81 mol) was added through the gas dispersion tube with stirring at 10-20°C over 2 hrs. After completing the monomethylamine addition, the mixture was stirred at 20°C for 20 hrs. to complete the reaction. A thick, pale yellow slurry was obtained. At this time, the unreacted monomethylamine, methanol and some toluene were distilled from the mixture at 100mmHg over 8 hrs. The resulting slurry was rotary evaporated to give crude N,N'-dimethyl-3,3'-dithiodipropionamide (1058.9g, 100% yield), containing 5,000 ppm N-methyl-3-(N'-methyl)aminopropionamide. A portion of the crude product (353.0g was slurried in 784.5g toluene) and vacuum filtered through a 2,000 ml course sintered glass funnel to give a toluene wet cake (419.1g). The toluene wet cake was washed with cold (0°C) methanol (352.4g) to give the methanol wet cake (315.2g). The methanol wet cake was dried in a vacuum desiccator at ambient temperature to give the washed, dried amide intermediate (251.1g), 71% recovery), containing 400 ppm N-methyl-3-(N'-methyl)aminopropionamide.

Following the process steps 2, 3 and 4 described in Experiment 2 above, the dry N,N'-dimethyl-3,3'-dithiodipropionamide was converted to give 260g of 3-isothiazolone product (pH 2.1) with the following composition:

Components	
5-chloro-2-methyl-4-isothiazolin-3-one	12.0 % by wt.
2-methyl-4-isothiazolin-3-one	2.7 % by wt.
Nitrosamine	25 ppm
Nitrosamine precursor(s)	none detected

EXAMPLE 4 (Precursor Removal by Ion Exchange)

Unfiltered Laktane (Experiment 1 above) process N,N'-dimethyl-3,3'-dithiodipropionamide was rotary evaporated in the laboratory to constant weight. The dried intermediate contained 10,000 ppm N-methyl-3-(N'-methyl)aminopropionamide.

Conditioned Amberlyst 15 sulfonic acid ion exchange resin (22.2g of 45.1% w/w material in water, 10.0g of dry resin) was washed into a 50 ml burette (1 cm diameter) with methanol (25 ml). The resin was rinsed on the column with methanol (500 ml) to give a resin bed volume of 28 ml.

The dry intermediate was dissolved in methanol to give a 19.9% w/w solution. This solution was passed through the resin column at ambient temperature and atmospheric pressure at a flow rate of 9.21 bed volumes per minute. The resin became saturated with N-methyl-3-(N'-methyl)aminopropionamide and break-through occurred after collecting 34 bed volumes. The total quantity of methanolic solution treated up to the break-through point was 737.2g. Rotary evaporation of

the eluent allowed recovery of the crude N,N'-dimethyl-3,3'-dithiodipropionamide (146.5g, 99.9% recovery), containing 380 ppm N-methyl-3-(N'-methyl)aminopropionamide. This crude product, when converted to a nitrate-stabilized 3-isothiazolone composition by the procedure of Example 1(b) results in a composition in accordance with the invention.

EXAMPLE 5 (Precursor Removal by Ion Exchange)

Into a one-liter, 4-necked flask equipped with a mechanical stirrer, thermometer, gas dispersion tube and dry ice condenser with nitrogen inlet adapter, was placed dimethyl-3,3'-dithiodipropionate (215.5g, 0.904 mol) and methanol (118.0g). The apparatus was purged with nitrogen and the mixture was cooled to ~10°C. Monomethylamine (70.0g, 2.25 mol) was added through the gas dispersion tube with stirring at 10-20°C over 2 hrs. After completing the addition, the mixture was stirred at 20°C for 20 hours. to complete the reaction. A thick, pale yellow slurry was obtained. At this time the unreacted monomethylamine and some methanol were distilled from the mixture at ~100mmHg. After distillation, a portion of the slurry (17.2g) was rotary evaporated to constant weight (8.0g), giving the concentration of crude product in the slurry at 47% w/w. The 47% w/w slurry was 436.0g, corresponding to 204.9g of crude N,N'-dimethyl-3,3'-dithiodipropionamide (96% yield). The dry, crude product contained 9,000 ppm N-methyl-3-(N'-methyl)aminopropionamide.

Conditioned Amberlyst 15 sulfonic acid ion exchange resin (22.2g of 45.1% w/w material in water, 10.0g of dry resin) was washed into a 50 ml buret (1 cm diameter) with methanol (25 ml). The resin was rinsed

on the column with methanol (500 ml) to give a resin bed volume of 28 ml.

The 47% w/w slurry in methanol was further diluted with methanol to provide a 20.0% w/w solution. This solution was passed through the resin column at ambient temperature and atmospheric pressure at a flow rate of 0.21 bed volumes per minute. The resin became saturated with N-methyl-3-(N'-methyl)aminopropionamide and break-through occurred after collecting 18 bed volumes of eluent. The total quantity of methanolic N,N'-dimethyl-3,3'-dithiodipropionamide solution treated up to the break-through point was 315.0g (63.0 of AI). Rotary evaporation of the eluent allowed recovery of the crude N,N-methyl-3,3'-dithiodipropionamide (63.0g, 100% recovery), containing 300 ppm N-methyl-3-(N'-methyl)aminopropionamide.

Following the procedure described in Example 2, 73.3g of the above-mentioned intermediate was chlorinated, filtered and neutralized to give 217.5g of Tech grade product.

A 60g sample of this Tech grade product was formulated with 29.4g of $Mg(NO_3)_2 \cdot 6H_2O$ and 7.8g of water. The formulated product was heat-treated at 95°C for 4 hours, cooled and filtered to give about 97g of 3-isothiazolone with the following composition:

5-chloro-2-methyl-4-isothiazolin-3-one	11.7 % by wt.
2-methyl-4-isothiazolin-3-one	3.5 % by wt.
Nitrosamine, ppm	33
Nitrosamine precursor(s)	none detected

EXAMPLE 6 (Inhibition of Precursor by Nucleophilic Scavenger)

Following the procedure of Experiment 2, Step 1, dimethyl-3,3'-dithiodipropionate (212.5g, 0.892 mol), methyl-3-mercaptopropionate (18.4g, 0.153 mol) and monomethylamine (69.0g, 2.22 mol) were reacted. The intermediate slurry was rotary evaporated to give crude N,N'-dimethyl-3,3'-dithiodipropionamide (224.1g, 98% crude yield), containing 1,000 ppm N-methyl-3-(N'-methyl)aminopropionamide. When the above steps were repeated using higher levels of a nucleophilic mercapto scavenger, the results established an essentially proportional reduction of nitrosamine precursor as higher concentrations of nucleophilic scavenger were used. In this manner, there is produced an essentially nitrosamine-free and nitrosamine precursor-free 3-isothiazolone composition in accordance with the invention.

EXAMPLE 7 (Inhibition of Precursor by Mercaptan Reactant Route)

Step 1: Preparation of N-methyl-3-mercaptopropionamide (MMPA)

Into a one-liter, 4-necked flask equipped with a mechanical stirrer, thermometer, gas dispersion tube, and dry ice condenser with nitrogen inlet adapter, was placed methyl-3-mercaptopropionate (MMP, 504.7g, 4.20 mol). The vessel was purged with nitrogen and the liquid was cooled to 10°C. Monomethylamine (163.0g, 5.25 mol) was added through the gas dispersion tube with stirring at 10-20°C over 1 hr. After completing

the addition, the mixture was stirred at 20°C for 20 hrs. to complete the reaction. At this time the methanol by-product and unreacted monomethylamine were distilled from the mixture at ~100mmHg. The resulting mixture was rotary evaporated to give crude N-methyl-3-mercaptopropionamide (500.8g, 100% yield), containing <30 ppm N-methyl-3-(N'-methyl)aminopropionamide.

Step 2: Chlorination

The procedure described in Experiment 2 was modified in that N-methyl-3-mercaptopropionamide (MMPA) was used in place of N-N'-dimethyl-3,3'-dithiodipropionamide. Thus, a 31% solution of N-methyl-3-mercaptopropionamide in toluene and Cl_2 were fed concurrently at a molar feed ratio of about 3.2.

To 59.5g of a toluene heel, 398.9g of 31% MMPA solution was charged over a period of 55 minutes at a rate of 7.1g per minute, while a 220g of Cl_2 was fed concurrently at a feed rate of 4.0g per minute.

Step 3: Filtration and Neutralization

Following the procedure described in Experiment 2, the chlorination slurry made above was worked-up and neutralized to give 355g of Technical grade 3-isothiazolone with the following composition:

5-chloro-2-methyl-4-isothiazolin-3-one	16.0% by wt.
2-methyl-4-isothiazolin-3-one	5.3% by wt.

Step 4: Formulation and Heat Treatment (Stabilization)

Following the procedure described in Experiment 2, a 200g portion of the Tech grade material made above was formulated by adding 87.7g $Mg(NO_3)_2 \cdot 6H_2O$ and 2.1g water. The formulated product was heat-treated, cooled and filtered to give 289g of 3-isothiazolone product with the following composition:

5-chloro-2-methyl-4-isothiazolin-3-one	12.2% by wt.
2-methyl-4-isothiazolin-3-one	3.9% by wt.
Nitrosamine	3.9 ppm
Nitrosamine precursor(s)	none detected

EXAMPLE 8 (Preparation of N-(n-octyl)-3-mercaptopropionamide by Mercaptan Reactant Route)

In a small multi-necked reaction vessel equipped with a magnetic stirrer and gas inlet was placed isopropanol (2 ml), methyl-3-mercaptopropionate (2.0g, 16.64 mmol), and n-octylamine (2.19g, 16.94 mmol). The reaction vessel was connected to a trap containing bleach to trap mercaptan vapors, and the reaction was stirred for 19.5 hours while the reaction temperature was held at 30-35°C. Methylene dichloride was added and the crude product was transferred to a round bottom flask. Evaporation of the solvent under reduced pressure yielded crude N-(n-octyl)-3-mercaptopropionamide as an oily white solid in essentially quantitative yield.

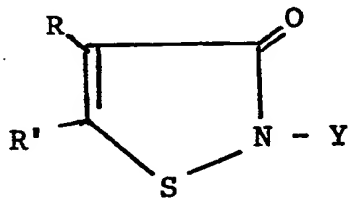
The N-(n-octyl)-3-mercaptopropionamide thus prepared is converted to a composition containing the corresponding 2-n-octyl-isothiazolin-3-one substantially free of nitrosamine and nitrosamine precursor, i.e. a composition in accordance with the invention.

EXAMPLE 9 (Preparation of N-propyl-3-mercapto-propionamide by Mercaptan Reaction Route)

In a small multi-necked reaction vessel equipped with a magnetic stirrer, reflux condenser, and gas-inlet was placed isopropanol (2 ml), n-propylamine (1.00g, 16.92 mmol), and methyl-3-mercaptopropionate (2.0g, 16.64 mmol). The reaction vessel was connected to a trap containing bleach, and the reaction was stirred at 30-35^{o}C for 19.5 hours. The crude reaction mixture was concentrated under reduced pressure to remove excess amine, solvent and methanol. A light yellow liquid was obtained which was essentially all N-propyl-3-mercapto-propionamide. The N-propyl-3-mercaptopropionamide thus prepared is converted to a composition containing the corresponding N-propylisothazolin-3-one substantially free of nitrosamine and nitrosamine precursor, i.e. a conposition in accordance with the invention.

CLAIMS:

1. A biocidal, or biostatic composition containing (1), as an active component, at least one 3-isothiazolone, (2) a medium for the 3-isothiazolone and (3) a nitrosating agent capable, on treating the composition, of converting, to a nitrosamine, any nitrosamine secondary or tertiary amine precursor present therein, said 3-isothiazolone being of Formula I below:



(I)

wherein R and R' are the same or different and represent hydrogen, halogen or (C_1-C_4) alkyl and Y is (C_1-C_8) alkyl, (C_3-C_6) cycloalkyl aralkyl of up to 8 carbon atoms or optionally substituted phenyl groups, and characterised in that the impurity content, if any, in the composition of nitrosamine(s) plus nitrosamine precursor(s) is less than 15 ppm (on a weight basis) of 3-isothiazolone(s) of Formula I.

2. A composition as claimed in Claim 1, wherein the nitrosating agent is a nitrate salt present in an amount sufficient to stabilize the 3-isothiazolone against ring cleavage.

3. A composition as claimed in Claim 1 or 2, wherein said impurity content is less than 7.5 ppm.

4. A composition as claimed in any preceding claim wherein the medium contains water and the 3-isothiazolone is water-soluble.

5. A composition as claimed in any preceding claim, wherein Y is methyl, ethyl, propyl or butyl, R is hydrogen and R' is halogen or hydrogen.

6. A composition as claimed in Claim 5, containing one or both of the 3-isothiazolones of Formula I wherein R is

hydrogen, R' is hydrogen or chlorine and Y is methyl.

7. A composition as claimed in Claim 7, wherein the 3-isothiazolone content comprises a mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one, the mixture containing 60-90% by weight of the chloro compound.

8. A composition as claimed in any preceding claim wherein said impurity content is less than 3 ppm.

9. A process wherein a biocidal or biostatic composition containing at least one 3-isothiazolone of Formula I in Claim 1 is subjected to nitrosating conditions such that a nitrosamine secondary or tertiary amine precursor, if present, would be converted to a nitrosamine, wherein the composition subjected to nitrosating conditions contains, if any, no more than that amount of nitrosamine precursor(s) which, after nitrosation, would result in an impurity content of nitrosamine(s) plus nitrosamine precursor(s) of less than 15 ppm (on a weight basis) of 3-isothiazolone(s) of Formula I.

10. A process as claimed in Claim 9, wherein the nitrosating conditions involve treatment with an amount of a nitrate salt sufficient to stabilize the 3-isothiazolone(s) against ring cleavage.

11. A process as claimed in Claim 9 or 10, wherein said impurity content is less than 7.5 ppm.

12. A process as claimed in any of Claims 9 to 11 wherein the 3-isothiazolone content comprises 5-chloro-2-methyl-4-isothiazolone and/or 2-methyl-4-isothiazolin-3-one.

13. A process as claimed in any one of Claims 9-12, wherein the 3-isothiazolone content comprises a mixture as defined in Claim 7.

14. A process as claimed in any of Claims 9 to 13, wherein said impurity content is less than 3 ppm.

15. A process as claimed in any one of Claims 9 to 14, wherein (1) the 3-isothiazolone is prepared by cyclization of an intermediate product containing a diamide of the

formula S $\underset{1-3}{\text{———}}\left(\underset{Z}{\overset{X}{\overset{|}{C}}}\text{HCH}\overset{O}{\overset{\|}{C}}\text{NHY}\right)_2$ where X and Z are hydrogen or (C_1-C_4) alkyl and Y is as defined in Claim 1 and (2) any nitrosamine precursor is removed wholly or in part from said intermediate product by (a) ion-exchange, (b) recrystallization and/or (c) solvent extraction.

16. A process as claimed in any one of Claims 9 to 14, wherein the presence of nitrosamine precursor(s) is avoided or reduced (1) by preparing the 3-isothiazolone from an intermediate product as defined in Claim 15 and (2) forming said intermediate product by the reaction of an appropriate disulfide and amine in the presence of a nucleophilic scavenger.

17. A process as claimed in any one of Claims 9 to 14, wherein the presence of nitrosamine precursor(s) is avoided or reduced by cyclization, with a halogenating agent, of a mercapto-amide of the formula $\underset{Z}{\overset{X}{\overset{|}{C}}}\text{HCH}\overset{O}{\overset{\|}{C}}\text{NHY}$ where X and Z are as defined in Claim 15 and Y is as defined in Claim 1.

18. A process as claimed in Claim 16 or 17 wherein (a) ion exchange, (b) recrystallisation and/or (c) solvent extraction is/are also used to effect partial or complete removal of nitrosamine precursor(s).

19. A cosmetic (including toiletry) or pharmaceutical preparation containing a biocidal or biostatic amount of a composition as claimed in any one of Claims 1 to 8 or a composition when prepared by a process as claimed in any one of Claims 9 to 18.